

# Do clinical characteristics and metabolic markers detected on positron emission tomography/computerized tomography associate with persistent disease in patients with in-operable cervical cancer?

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**Abstract** The objective of this retrospective study was to evaluate the prognostic significance of volume-based metabolic markers of PET/CT along with clinical characteristics in patients with in-operable cervical carcinoma.

**Methods** Fifty-eight patients with cervical carcinoma (stage IIB–IVB) underwent FDG PET/CT for pretreatment evaluation and included in this study. Patients were staged according to International Federation of Gynecology and Obstetrics [FIGO] system. After chemoradiation therapy, patients were evaluated for persistent disease (PD) by clinical examinations, smear tests, pelvic MRI and PET/CT. Based upon follow-up results, clinical characteristics (patient age, tumor histology, FIGO stage) and PET/CT findings such as presence of PET-positive pelvic/para-aortic lymph nodes (LN), metabolic tumor volume (MTV), total lesion glycolysis (TLG), maximum standardized uptake values (SUVmax) of tumor and lymph nodes were analyzed for disease persistence. Survival analysis for disease-free survival and overall survival was performed with Kaplan–Meier method using PET findings and clinical characteristics.

**Results** At the time of last follow-up (mean:  $22 \pm 12.6$  months, range 6–48), 38 patients (65 %) had PD, 20 patients (35 %) had no evidence of disease (NED). Patient age, tumor histology, MTV, TLG and tumor SUVmax did not differ between groups. The frequency of PET-positive pelvic/para-aortic lymph nodes (84 vs. 60 %,  $p = 0.03$ ), LN

SUVmax (10.2 vs. 6.5,  $p = 0.02$ ), and FIGO stage differed significantly between PD and NED groups. Cox proportional hazards model demonstrated advanced FIGO stage and the presence of PET-positive para-aortic LN were independent predictors for PD. Both disease-free survival and overall survival curves showed progressive worsening as the disease advanced,  $p = 0.015$ . PET LN status was the most important prognostic indicator for disease-free survival and overall survival. The worst outcome curves were detected for patients with PET-positive para-aortic lymph nodes among all patients,  $p = 0.03$ .

**Conclusion** Advanced FIGO stage and the presence of FDG-avid para-aortic lymph nodes on pretreatment PET/CT are significant prognostic biomarkers for PD and decreased overall survival in patients with in-operable cervical carcinoma independent from MTV, TLG, tumor and lymph node SUVmax.

**Keywords** Cervical cancer · PET/CT · Metabolic tumor volume · Total lesion glycolysis · Prognosis · SUVmax

## Introduction

Cervical carcinoma is the third most frequently diagnosed malignancy in women worldwide and is one of the leading causes of cancer deaths [1, 2]. Traditional prognostic factors in cervical carcinoma include patient age, performance status, clinical tumor stage, lymph node involvement and treatment skills. However, today, many clinical factors, pathological characteristics and/or metabolic parameters of the tumor are proven to correlate with clinical outcome [2–10].

In recent years, the role of F18-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in the staging and management of

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gynecological cancers has been increasing. Strong evidence from a growing number of research support the value of PET/CT in the pretreatment work-up of patients with cervical cancer, as the modality with higher sensitivity and positive predictive value compared to CT and MRI [11–13]. In addition, in our previous report, we observed that PET/CT provides the unique advantage to detect both para-aortic lymphatic involvement and distant metastasis and contributed to patient management plan in a considerable proportion of patients with cervical cancer [11]. Furthermore, beyond accurately determining disease extent, FDG PET/CT provides prognostic information by quantifying FDG uptake in terms of standardized uptake value (SUV) and measuring volume-based metabolic parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) [14–17].

SUV, as a semi-quantitative measurement of FDG uptake provides intrinsic molecular-biological information of tumors. Such that, high SUV<sub>max</sub> of the primary tumor predicts a worse clinical outcome [9, 17–21]. MTV defined as the volume of tumor tissues with increased FDG uptake, is a volumetric and quantitative measurement of tumor cells with high glycolytic activity and reflects the tumor burden. TLG is another volume-based metabolic parameter which represents the metabolic burden of disease, and depends on both tumor volume and glucose utilization rate. Recently, the use of MTV and TLG was suggested as reliable parameters in providing more details about the status of disease in various types of cancers, such as lung tumors, cervical cancers and head-and-neck cancers [21–25].

Up-to-date, several studies are reported concerning the prognostic significance of many metabolic and histopathological parameters in cervical cancer patients. Our group previously evaluated the clinical impact of PET/CT on the pretreatment work-up of a similar patient population with locally advanced cervical cancer and found that the presence of FDG-avid lymph nodes was inversely correlated with prognosis in univariate analysis [11]. Nevertheless, still, there is some controversy and confusion in the literature about which metabolic parameters may be genuinely prognostic when analyzed together with patients' clinical characteristics for widely varied patient populations [14–17]. For this purpose, we aimed to further evaluate indicators related to poor prognosis in patients with inoperable cervical carcinoma.

In this study, by analyzing volume-based metabolic parameters of PET/CT such as MTV, TLG, tumor SUV<sub>max</sub>, lymph node SUV<sub>max</sub>, and the presence of FDG-avid lymph nodes in a multivariate analysis together with clinical characteristics such as age at diagnosis and clinical FIGO stage, we aimed to establish a clinical and metabolic imaging profile to identify prognostic factors associated

with poor disease-free survival and overall survival in a series of 58 patients treated and followed up in our institution.

## Methods

Fifty-eight patients with in-operable cervical carcinoma (FIGO stage IIB–IVB), who underwent FDG PET/CT imaging for pretreatment evaluation, were included in this retrospective study. Patients with early stage cervical cancer (FIGO stage IA–IIA), patients with a prior history of neoadjuvant chemotherapy for cervical cancer, patients with previous diagnosis of another malignant disease, and patients with a follow-up duration less than 3 months were excluded from the study.

This study was approved by the ethics committee of our institution.

Patients were imaged on an integrated PET/CT scanner (Siemens Biograph 6-True Point PET/CT systems). Patients were fasted for at least 6 h prior to injection of 5.3 MBq/kg (144  $\mu$ Ci/kg)  $^{18}$ F-FDG. The blood glucose levels were less than 150 mg/dl in all patients at the time of the FDG injection. Unenhanced CT images were acquired for attenuation correction from the base of the skull to distal thigh using 3 mm slice thickness and calculated effective mAs due to patient weight. The PET and CT images were reviewed on a workstation (Leonardo, Siemens Medical Solutions) in all standard planes along with maximum-intensity-projection images and were analyzed visually and quantitatively by two reviewers experienced in interpreting PET/CT scans. Findings were recorded by consensus.

The maximum standardized uptake value was used to quantify FDG uptake. SUV<sub>max</sub> was calculated using the following formula:

$$\text{SUV}_{\text{max}} = \text{C}_{\text{max}} \times \text{TBW}/\text{IA}$$

where, C<sub>max</sub> is the activity concentration in the voxel of highest tumor activity (Bq/ml), TBW is the total body weight (kg), and IA is the injected activity (kBq).

To provide the most accurate measurement of SUV<sub>max</sub>, voxels were created large enough to maintain tumor inside the boundaries, and maximum care was accomplished to avoid “spill-in” from adjacent structures with intense FDG uptake. For this reason, images were acquired immediately after voiding.

Tumor volume was measured from attenuation-corrected FDG PET/CT images using an SUV-based automated contouring program (Syngo MI applications, Volumetric Analysis 6.0.14.4, Siemens Medical Solutions). The boundaries of tumor were drawn large enough to incorporate each target lesion in the axial, coronal, and

sagittal FDG PET/CT images. Depending on previous data, a fixed threshold value of 40 % of SUVmax was used [26]. The voxels presenting SUV intensity greater than that of 40 % of SUVmax within the contouring margin were incorporated to define the tumor volumes.

Total lesion glycolysis was calculated as the sum of the product of SUVmean and MTV of primary tumor (TLG = sum of [SUVmean × MTV]).

The size and FDG uptake in pelvic and para-aortic lymph nodes were evaluated by PET/CT. It is known that for tumors smaller than the reconstructed spatial resolution, the partial volume effect may result in a more than 50 % underestimation of the true FDG concentration [27]. Because standard uptake values can be affected by many technical factors, and besides, SUV measurements can be underestimated by partial volume effect, the presence of focal increased FDG uptake in the lymph nodes, regardless of its size and standard uptake value, was considered as “PET positive” and suggestive of nodal involvement.

All patients were staged clinically according to International Federation of Gynecology and Obstetrics [FIGO] staging criteria. All patients were treated with concurrent chemotherapy and radiation therapy following the recommendations in National Comprehensive Cancer Network (NCCN) guidelines [28]. Patients with stage IIB–IVA disease received a total of 45 Gy external beam radiation therapy (EBRT) (in conventional fractionation of 1.8 Gy daily). Starting from the third week of external radiation therapy, a total of 40 Gy intracavitary brachytherapy was administered to Point A. In addition, patients with FDG-avid para-aortic lymph nodes received 45 Gy EBRT to para-aortic region. All patients with stage IIB-stage IVA disease received concomitant cisplatin-based chemotherapy (40 mg/m<sup>2</sup> weekly for 6 cycles). Patients with stage IVB disease received systemic chemotherapy and palliative radiation therapy as indicated for system management.

Patients had follow-up examinations approximately every 2 months for the first 6 months and every 3 months for the next 2 years. Pap smear tests, abdominal and pelvic MRI and/or PET/CT were repeated 3 months after the completion of treatment and when warranted by clinical examinations or symptoms. The sites and findings related with malignant disease were recorded. Persistent pelvic disease was defined as residual or recurrent cervical tumor, lymph nodes, or both.

#### Statistical analysis

Clinical characteristics and PET parameters were analyzed for correlation with outcome data. The association of disease persistence with clinical characteristics and PET parameters were analyzed by univariate analysis using a Chi square test. Tumor SUVmax was compared to MTV

using regression analysis. The Cox proportional hazards model was used for multivariate analyses. Disease-free survival and overall survival were calculated using the Kaplan–Meier method. The statistical analyses were performed using commercial software (SPSS 13.0). *p* values <0.05 were considered to be statistically significant.

## Results

Patient and tumor characteristics are listed in Table 1.

The mean age was 57.7 ± 14.5 years in our patient population with a range of 26–86 years. 52 patients had squamous, 1 patient had adenosquamous and 5 had nonsquamous carcinoma. According to FIGO staging criteria, 19 patients had stage IIB, 4 patients had stage IIIA, 6 patients had stage IIIB, 12 patients had stage IVA, and 17 patients had stage IVB disease.

The mean follow-up duration was 22 ± 12.6 months with a range of 6–48 months. At the time of last follow-up, 20 patients (35 %) had no evidence of disease (NED group). Thirty-eight patients (65 %) had persistent disease (PD) and defined as PD group. 13 patients had pelvic disease (either residual/recurrent tumor or lymph nodes) and 25 patients had progressive disease with distant metastases. Among PD group, 8 patients with progressive disease died due to cancer-related causes.

Mean patient age at the time of diagnosis was 61.1 years in NED group and 55.9 years in PD group. Groups were comparable in terms of patient age (*p* = 0.2). Likewise,

**Table 1** Patient characteristics

Characteristics	
Mean age at diagnosis (years)	57.7 ± 14.4 (range 26–86)
Follow-up time (months)	15 ± 8 (range 6–36)
FIGO stage	
IIB	19
IIIA	4
IIIB	6
IVA	13
IVB	16
Histology	
Squamous	52
Adenosquamous	1
Nonsquamous	5
Lymph node status	
None	14
Pelvic lymph nodes	23
Para-aortic lymph nodes	3
Pelvic and para-aortic lymph nodes	18

tumor histology did not differ significantly between groups ( $p = 0.5$ ) (Table 2).

We observed that clinical FIGO stage correlated with patient follow-up information; such that, high clinical FIGO stage was associated with disease persistence on follow-up. The number of patients with FIGO stage II–III–IV was 7–6–25 in PD group and 12–4–4 in NED group, respectively. Patients in NED group appeared to have lower FIGO stages than patients with PD group,  $p = 0.002$ .

Forty-four patients had PET-positive lymph nodes. Of these, 23 patients had pelvic-only nodes whereas 21 patients had both pelvic and para-aortic nodes. The average size of lymph nodes in our patient population was  $0.7 \pm 0.2$  cm within a range of 0.4–2 cm. The average SUVmax of the lymph node was  $7.5 \pm 4.1$  within a range of 4.1–22.8.

The frequency of FDG-avid pelvic and/or para-aortic lymph nodes was higher in PD group compared to NED (84.2 vs. 60 %, respectively),  $p = 0.03$ . For further analysis, the localizations of the PET-positive lymph nodes were evaluated for the association of PD. Patients with FDG-avid para-aortic lymph nodes had higher risk to develop PD than patients with pelvic-only nodes and patients without lymph nodes ( $p = 0.005$ ).

Univariate analysis revealed significant difference between SUVmax of the most FDG-avid lymph nodes among PD and NED groups. The average of lymph node SUVmax was significantly higher in PD group compared to NED group ( $10.2 \pm 4$  vs.  $6.5 \pm 3.8$ , respectively,  $p = 0.02$ ).

We observed that, tumor SUVmax was comparable in between NED and PD groups (Table 2). The average of cervical tumor SUVmax was  $17.5 \pm 6.1$  in PD group and

$17.9 \pm 6.5$  in NED group ( $p = 0.9$ ). We observed no association between tumor SUVmax and disease persistence. Similarly, we observed no differences in terms of MTV between NED and PD groups ( $106.9 \pm 128$  vs.  $41.5 \pm 22.8$  cm<sup>3</sup>, respectively,  $p = 0.1$ ). We detected that tumor SUVmax was not correlated with MTV, with the correlation coefficient ( $R^2$ ) = 0.05. Likewise, we observed that TLG did not differ between PD group and NED group. The average of TLG in PD group was  $898 \pm 1160$ , whereas  $381 \pm 232$  in the NED group,  $p = 0.3$ .

A Cox proportional hazards model for disease persistence in patients with in-operable cervical cancer was performed including the presence of PET-positive pelvic and para-aortic lymph nodes, the location of lymph nodes and lymph node SUVmax and FIGO stage (Table 3). Cox regression analysis revealed that stage IV disease and the presence of PET-positive para-aortic lymph nodes were independent predictors of disease persistence on follow-up independent from SUVmax. We found that patients with PET-positive para-aortic lymph nodes had 5.3 times greater risk to develop PD [hazard ratio (HR): 5.3, 95 % CI 2.08–12.9] compared to others. Similarly, hazard ratio for developing PD was calculated as 3.3 for patients with stage IV disease compared to stage IIB (95 % CI 1.3–8.5) (Table 3).

The Kaplan–Meier curves for disease-free survival and overall survival indicated better outcomes for patients without PET-positive lymph nodes compared to patients with pelvic-only nodes and patients with para-aortic nodes. The worst outcome curve was detected for patients with PET-positive para-aortic lymph nodes among all patients,  $p = 0.03$  (Fig. 1). Similarly, disease-free survival and overall survival curves showed progressive worsening as the disease advanced. Better outcome results were demonstrated on Kaplan–Meier curves for stage II patients than stage III patients and stage IV patients, respectively,  $p = 0.015$  (Fig. 2).

**Table 2** Comparison of clinical characteristics and metabolic parameters between groups

	PD	NED	<i>p</i>
Mean age at diagnosis	55.9 ± 14.7	61.1 ± 13.6	0.2
Tumor histology			
Squamous	33 (87 %)	19 (95 %)	0.5
Nonsquamous	1 (3 %)	0	
Adenosquamous	4 (11 %)	1 (5 %)	
FIGO staging			
II	7 (18 %)	12 (60 %)	0.0015
III	6 (16 %)	4 (20 %)	
IV	25 (66 %)	4 (20 %)	
Frequency of LN	32 (84.2 %)	12 (60 %)	0.04
Frequency of para-aortic LN	17 (45 %)	3 (15 %)	0.03
LN SUVmax	10.2 ± 4	6.2 ± 3.8	0.02
Tumor SUVmax	17.5 ± 6.1	17.9 ± 6.5	0.9
Tumor volume (cm <sup>3</sup> )	106.9 ± 128.7	41.5 ± 22.8	0.1
TLG	898 ± 1160	381 ± 232	0.3

PD persistent disease, NED no evidence of disease, LN lymph node

## Discussion

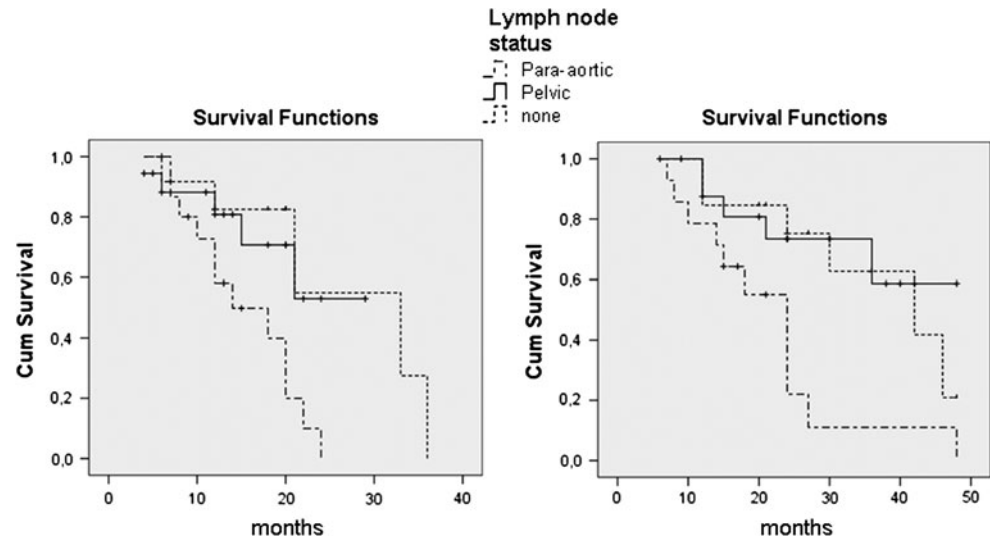
In this study, we examined the association of PET-based volumetric and metabolic parameters and clinical characteristics

**Table 3** Cox proportional hazards model for disease persistence

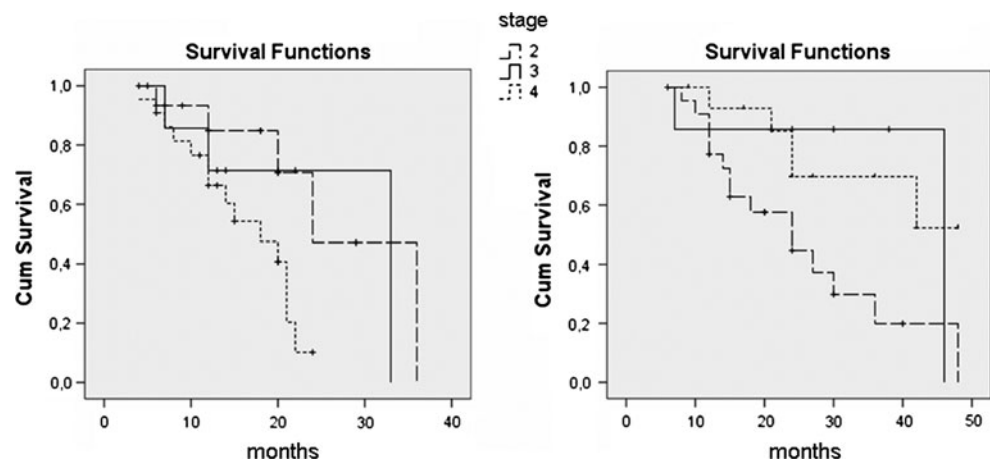
	<i>p</i>	HR	95 % CI
Presence of pelvic LN	0.1	2.4	0.7–7.6
Presence of para-aortic LN	0.03	5.3	2.08–12.9
FIGO stage	0.01	3.3	1.3–8.5
LN SUVmax	0.2	0.9	0.87–1

LN lymph node, HR hazard ratio, CI confidence interval

**Fig. 1** The Kaplan–Meier curves for disease-free survival and overall survival divided by the presence and the location of PET-positive lymph nodes



**Fig. 2** The Kaplan–Meier curves for disease-free survival and overall survival show progressive worsening as the disease advance. Better outcome results are seen for stage II patients than stage III patients and stage IV patients, respectively



with disease persistence in patients with in-operable cervical carcinoma. Our results suggested that advanced FIGO stage and the presence of FDG-avid para-aortic lymph nodes on pretreatment PET/CT were significantly associated with poor disease-free survival and overall survival.

Cervical cancer is the only gynecological cancer clinically staged according to FIGO staging system [29]. Even though there is growing debate in the literature on the prognostic value of FIGO staging system for it does not rely on surgical-pathological findings and lymph node status, the results of this study demonstrate the prognostic value of FIGO staging and its association with disease persistence in patients with in-operable cervical cancer [30–32]. In this study, we observed that patients with stage IV disease had 3.3 times greater risk to develop PD, lower disease-free survival and overall survival compared to patients with earlier stage disease.

In this study, we found that patients with PET-positive para-aortic lymph nodes had 5.3 times higher risk developing PD after chemoradiotherapy. Moreover, our results

indicated that, the presence of FDG-avid para-aortic lymph nodes in pretreatment PET/CT was more predictive of clinical outcome than advanced FIGO stage. These findings supported previously published data, in which lower overall survival rates were reported in patients with para-aortic lymph node metastasis [16, 30, 33, 34].

In this regard, the clinical impact of PET/CT imaging in the pretreatment work-up of patients with cervical carcinoma comes into prominence. Because para-aortic lymph nodes are beyond the standard radiation fields, accurate assessment of para-aortic lymph node metastasis is crucial for determining the extent of radiotherapy and improving patient survival [35–37]. Compared to CT and MRI, PET/CT takes a step further in the detection of para-aortic lymph nodes. In our study, the size of FDG-avid lymph nodes ranged within 0.4–2 cm. This means that, lymph nodes smaller than 1 cm in size would have falsely considered as negative on CT and MRI if these nodes were not evaluated with PET/CT.

In our previous research, we observed that PET/CT has led to modifications in the extent of the radiotherapy field

in 34 % of patients and to major alterations in treatment plans in 23 % of patients with cervical carcinoma [11]. In addition, as a preliminary result, we observed that the frequency of the presence of FDG-avid para-aortic lymph nodes was significantly higher among patients with poor prognosis in univariate analysis [11]. Based on our previous study, in the present study, we further analyzed all PET-based volumetric and metabolic findings together with clinical characteristics in a detailed multivariate analysis depending on a mean follow-up duration of  $22 \pm 12.6$  months.

Our results indicated that in patients with in-operable cervical carcinoma, factors such as TLG, MTV, and tumor SUVmax, which were previously reported to associate with poor prognosis in patients with early stage disease, fail to associate with patient prognosis on multivariate analysis [5, 9, 32]. In addition, even though the average SUVmax of FDG-avid lymph nodes was significantly higher in patients with PD compared to NED group, the results of the multivariate analysis indicated that there was no association between lymph node SUVmax and overall survival. Even though authors have clarified that tumor volume, high tumor and lymph node SUVmax were predictive of unfavorable prognosis for cervical cancer patients [4, 9, 15–19, 26, 32]; we did not observe any associations of disease persistence with these parameters. However, these studies that demonstrate the association of defined metabolic parameters with poor patient outcome include patients with early stage cervical cancer [5, 7, 15, 16]. We considered that the discrepancy of our results from the former studies derived from the enrollment of in-operable patients and exclusion of patients with early stage disease. In this study, we observed that, having stage IV disease rather than stage II and stage III disease was associated with 3.3 times greater risk to develop PD. We considered that the association of lymph nodes' SUVmax with disease persistence which was previously reported to be associated with poor prognosis [10] and also seen in our univariate analysis must have been masked both by tumor stage and the location of PET-positive lymph nodes under multivariate Cox regression analysis.

Furthermore, strong evidences supporting our results are available in the literature. Recent data have suggested that, in patients with cervical cancer, the predictors of disease recurrence were clinical stage, lymph node status at the time of the initial diagnosis and tumor response after the completion of therapy [30, 37]. In a recent study, Yoo et al. [14] reported that neither SUVmax, nor MTV of the primary tumor associated with event-free survival in patients with cervical cancer. On the contrary, they found that TLG better predicted prognosis than did other volume-based PET parameters and FIGO staging was not

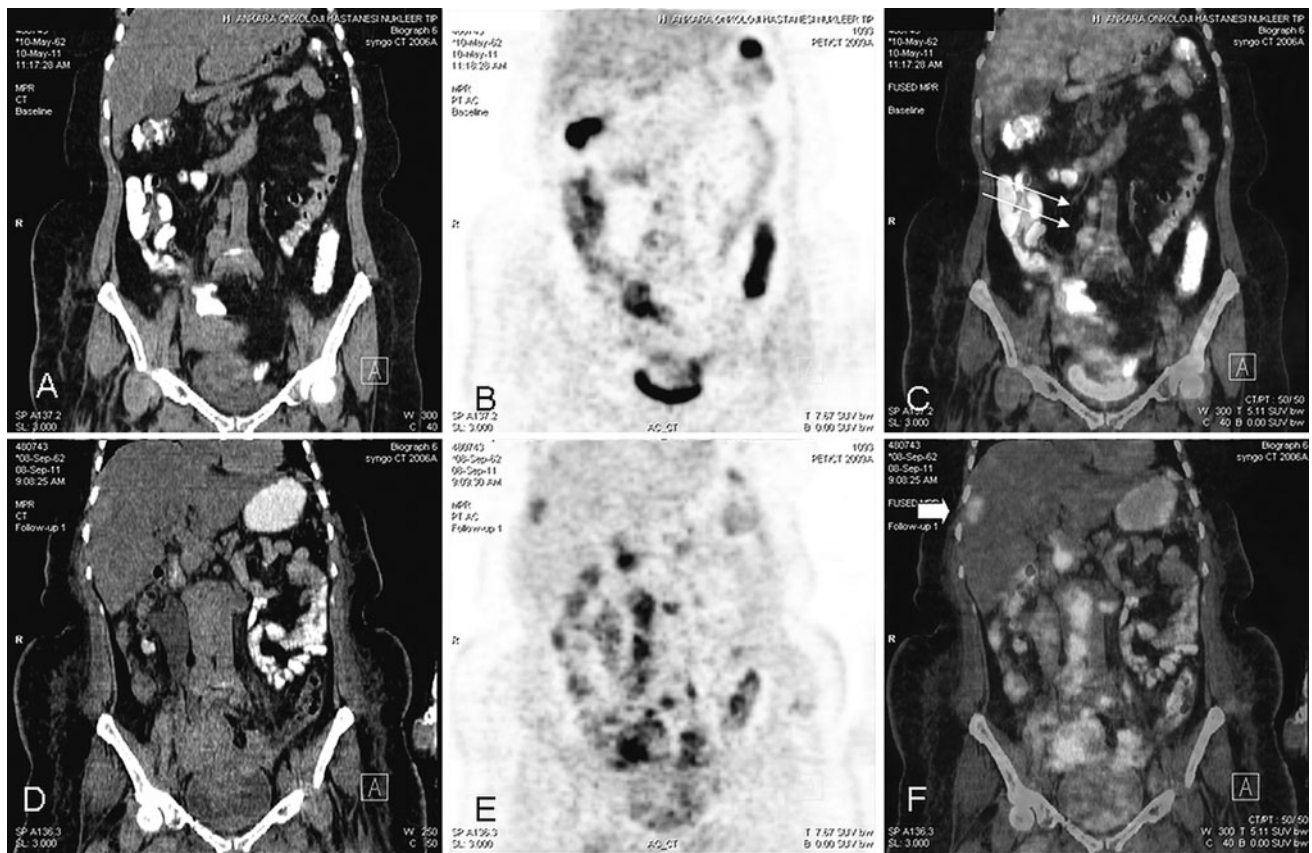
an independent prognostic factor after multivariate analysis [14].

In this regard, we considered that there are controversial results on the prognostic importance of PET-based volumetric and metabolic parameters in the literature. However, all reports agree on the fact that, the impact of PET/CT on the clinical management of patients with cervical cancer is its high sensitivity and accuracy in detecting disease extent in and outside the pelvis. We believe that separate prospective trials with larger homogeneous series of patients with early stage cervical cancer and patients with advanced stage disease are warranted to delineate the prognostic value of these volume-based metabolic parameters obtained by PET/CT.

We considered that when cervical tumors spread to para-aortic lymphatic chain or progress to a stage at which patients cannot benefit from curative surgery, metabolic parameters such as MTV, TLG, FDG uptake in tumor and metastatic lymph nodes which are previously demonstrated to be predictive of patient outcome, may become insignificant. Our results indicated that, regardless of SUVmax, the presence of FDG-avid para-aortic lymph nodes is the most important factor predictive of poor clinical outcome (Fig. 3).

The primary limitation of our study is that it is a retrospective study of 58 patients from a single center. In addition, the median follow-up duration after PET/CT was relatively short. Therefore, interpretation of the current study must be confined to short-term outcome, which implies a limited period of follow-up. Nevertheless, the results of this study are noteworthy because persistent cervical tumor on clinical examination performed 1–3 months after completion of therapy is previously shown to be associated with an increased risk of recurrence and poor overall survival [38]. Authors have found that posttreatment metabolic response and pretreatment lymph node status (as defined by 18F-FDG PET) were predictive of both cause-specific and progression-free survival after chemoradiation for cervical cancer [30, 39, 40]. However, analyses with larger number of cases and with a longer period of follow-up in prospective trials are required to validate the results of the present study.

In conclusion, we considered that when cervical malignancy advances to a surgically unamenable stage, the presence of para-aortic lymphatic metastasis and advanced FIGO stage appear as two major factors that adversely affect disease-free and overall survival. Regardless of SUVmax, patients with PET-positive para-aortic lymph nodes carry the highest risk to develop PD on follow-up. Thus, by successfully detecting extrapelvic disease, FDG PET/CT provides valuable long-term prognostic information in patients with in-operable cervical carcinoma and, in the future, may be used to guide additional therapy.



**Fig. 3** Upper row demonstrates coronal CT (a), PET (b) and fused PET/CT (c) slices in a 48-year-old female patient who underwent FDG PET/CT imaging for the initial staging of cervical carcinoma. The clinical FIGO stage was stage IIB. In PET/CT images, hypermetabolic para-aortic lymph nodes with SUVmax: 7.5 are seen (marked by *thin arrows*). The lower row demonstrates coronal CT (d),

PET (e) and fused PET/CT (f) slices of the follow-up study performed 15 months after the initial PET/CT. The progression of disease is clearly seen with widespread para-aortic lymph node metastasis in addition to liver metastasis (marked by *thick arrow*) with intense FDG uptake (SUV: 6.47). On follow-up, the patient died due to cancer-specific causes

**Conflict of interest** The authors declare that they have no conflict of interest.

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